

NAPM



NATIONAL ASSOCIATION OF PHARMACEUTICAL MANUFACTURERS

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March 30, 1999

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm 1061
Rockville, MD 20852

RE: Docket No. 98D-0994 - Guidance for Industry: BACPAC I: Intermediates in Drug Substance Synthesis --- Bulk Actives Postapproval Changes: Chemistry, Manufacturing, and Controls Documentation

The National Association of Pharmaceutical Manufacturers (NAPM) appreciates the opportunity to comment on this document. These comments represent the consensus of leading domestic and international manufacturers of bulk active pharmaceuticals and generic drug products.

We wish to compliment the Agency in producing a document that covers most issues regarding intermediates in drug substance synthesis. This document is quite complete and we are very pleased that the Agency has incorporated most of our industry concerns expressed previously. Our recommended changes to this document are intended to clarify the document and not rewrite it.

NAPM is the national trade organization representing manufacturers, distributors and repackagers of generic multisource prescription drugs, OTC drugs, dietary supplements and veterinary drugs. The organization prides itself in serving the needs of its members and has been heavily involved in legislative, legal, regulatory and technical issues.

We thank you for the opportunity to submit our comments. We hope that our comments are clear and welcome any questions that you may have.

Sincerely,

Leon Shargel

Leon Shargel, Ph.D.
Vice President and Technical Director

cc: Kasturi Srinivaschar, Ph.D.

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**Guidance for Industry: BACPAC I: Intermediates in Drug Substance Synthesis
Bulk Actives Postapproval Changes: Chemistry, Manufacturing, and Controls
Documentation [Docket No. 98D-0994]**

General Comments

This document is quite complete and covers most issues regarding intermediates in drug substance synthesis. This document provides a vehicle for drug substance manufacturers to make changes in their chemistry.

However, we have several comments listed below that have been recommended by our members.

Specific Comments:

p. 2, lines 32-39

NAPM appreciates the Agency's interest in decreasing the burden of certain notification procedures for change. However, drug substance manufacturers need clarification as to the responsibility for notifying the Agency in terms of filing an annual report, changes being effected (CBE) supplement, or a prior approval amendment. The responsibility for notification of the Agency should be on the ANDA holder. Does the Agency have a "time-line" for the response to a CBE?

p. 3, lines 75-77

Although details of the change may be kept confidential, at a minimum the holder of the master file should inform applicants of the type of filing recommended for their respective drug applications.

This sentence should be deleted. The drug master file holder is responsible for notifying applicants of the type of change. The finished dosage form manufacturer who is the holder of the ANDA is responsible for filing the appropriate documentation.

p. 4, lines 95-97

For example, if the drug substance is a mixture of isomers, then the same quantitative mixture should be obtained after the change.

This sentence should be changed to read, "For example, if the drug substance is a mixture of isomers, **then the specifications for the product after a change should be within the specifications for the original product.**

Rationale -- This document provides guidance for the synthesis of the intermediate and not the active drug substance.

p. 5, lines 123-124

The level of impurities should be assessed by comparing three postmodification batches to the range of historical data from ten premodification commercial batches.

This sentence should be changed to read, "The level of impurities should be assessed by comparing three postmodification batches to the range of historical data from ~~ten~~ **three** premodification commercial batches.

Rationale - Ten recent premodification batches may be difficult to obtain for small sales products. These low volume, occasionally produced products may have limited historical data. Since data may be obtained from three postmodification batches, then data from three premodification batches should be used for comparison.

p. 5, lines 137-138

1.b. Existing impurities, including residual organic solvents, are at or below the upper statistical limit of historical data.

This sentence should be changed to read, "Existing impurities, including residual organic solvents, are **within specifications or, if not specified**, are at or below the upper statistical limit of historical data.

Rationale -- Specifications are developed from historical data for the product prior to the change and then applied to the product after a change. Also, this statement is similar to p. 6, lines 149-151.

p. 5, lines 139-140

*1.c. **Total** impurities are at or below the upper statistical limit of historical data.*

This sentence should be changed to read, "Total impurities are **within specifications or, if not specified**, are at or below the upper statistical limit of historical data.

Rationale -- See rationale under p. 5, lines 137-138 above.

p. 6, lines 149-150

2.b. Existing impurities, including residual organic solvents, are within the stated limits or, if not specified, at or below the upper statistical limit of historical data.

This sentence should be changed to read, "Existing impurities, including residual organic solvents, are ~~within the stated limits~~ **specifications** or, if not specified, at or below the upper statistical limit of historical data."

Rationale -- See rationale under p. 5, lines 137-138 above.

p. 6, lines 152-153

2.b. Total impurities are within the stated limits or, if not specified, are at or below the upper statistical limit of historical data.

This sentence should be changed to read, "Total impurities are within the stated limits specifications or, if not specified, are at or below the upper statistical limit of historical data."

Rationale -- See rationale under p. 5, lines 137-138 above.

p. 6, lines 170-172

When equivalence cannot be demonstrated at commercial scale, the reviewing division should be contacted.

This sentence should be deleted.

Rationale -- The responsibility for contacting the Agency is on the ANDA holder and not the drug substance manufacturer.

p. 7, lines 173-177

Additional purification procedures (or repetition of an existing procedure on a routine basis) to achieve equivalence with prechange material after the final intermediate are not covered under BACPAC I. However, modified purification procedures prior to the final intermediate can be filed under BACPAC I (see section IV. C for process changes and section IV. D for multiple changes).

This paragraph should be changed to read, "Additional purification procedures, **modified purification procedures**, or repetition of an existing procedure on a routine basis to achieve equivalence with prechange material after the final intermediate ~~are not~~ can be covered under BACPAC I. ~~However, modified purification procedures prior to the final intermediate can be filed under BACPAC I~~ (see section IV. C for process changes and section IV. D for multiple changes).

Rationale -- These changes more clearly explains what changes may be covered under BACPAC I.

p. 7, line 200

- *Conforms to historical particle size distribution profile.*

This sentence should be changed to read, **"Is within the stated specifications or, if not specified,** conforms to historical particle size distribution profiles."

Rationale -- See rationale under p. 5, lines 137-138 above.

p. 7, lines 201-203

NAPM feels that the Decision Tree developed by the PhRMA BACPAC Work Group published in an article entitled, PhRMA Bulk Active Postapproval Changes (BACPAC) Decision Tree, *Pharmaceutical Technology*, pp. 68-76, September, 1998 is more appropriate than the Decision Tree that appears in this guidance. (A copy of this article is attached).

p. 8, lines 219-221

The new site, which may be within a single facility, within a contiguous campus, or in a different campus, should have similar environmental controls.

This sentence should be deleted.

Rationale -- Environmental controls may be different at different manufacturing sites. Environmental controls are considered on p 8, lines 225-226 which states that the manufacturing facilities should operate according to current GMPs.

p. 8, lines 227-229

Site changes within a single facility that fall within the scope of sections IV. A and IV. A. 1 need not be filed with the Agency, and equivalence testing as described in this document need not be carried out.

Change this sentence to read, "Site changes within a single facility **or contiguous campus** that fall within the scope of sections IV. A and IV. A. 1 need not be filed with the Agency, and equivalence testing as described in this document need not be carried out.

Rationale -- The addition of "or contiguous campus" makes the sentence more inclusive.

p. 9, lines 248-250

Delete the phrase, *"if relevant to the finished dosage form performance."*

Rationale -- The drug substance manufacturer does not have the responsibility to determine the relevance to the finished dosage form performance. The finished dosage form manufacturer is responsible for the performance for the drug product.

p. 9, lines 254-255

When equivalence is not established, the need for qualification of impurities and studies to ensure bioequivalence of the dosage form should be considered.

This sentence should be changed to read. "When equivalence is not established, the need for qualification of impurities and studies to ensure bioequivalence of the dosage form should be considered **by the applicant**."

Rationale -- The drug substance manufacturer does not have the responsibility for considering the need to perform a bioequivalence study. The finished dosage form manufacturer is responsible for this determination.

p. 9, lines 255-257

The additional data that should be submitted will depend on the individual case, and the appropriate review division(s) should be contacted for guidance.

This sentence should be changed to read. "The additional data that should be submitted **by the applicant** will depend on the individual case, and the appropriate review division(s) should be contacted for guidance."

Rationale -- The responsibility for notifying the Agency should be on the ANDA holder and not the drug substance manufacturer. Any additional data should be filed by the applicant.

p. 9, line 261, Filing Documentation

The guidance does not indicate whether the drug substance manufacturer or the finished dosage form manufacturer (i.e, ANDA holder) is responsible for filing documentation.

p. 10, lines 295-296

Delete the phrase, *"if relevant to the finished dosage form performance."*

Rationale -- The drug substance manufacturer does not have the responsibility to determine the relevance to the finished dosage form performance. The finished

dosage form manufacturer is responsible for the performance for the drug product.

p. 10, lines 305-306

NAPM does not understand how the outsourced intermediate is affected by the scale change. Does the drug substance manufacture need to report to the Agency if the outsource supplier has scaled up? Normally, a certificate of analysis is obtained from the outsource supplier.

p. 10, line 323

The term, "*significant change*," needs to be defined in this document.

p. 13, lines 371-373

p. 15, lines 414-416

p. 16, lines 453-455

p. 18, lines 507-509

This sentence needs further clarification as to the type of data required in the report. In addition, the guidance does not state where and when the report must be filed.

p. 13, lines 381-382

p. 15, lines 429-430

p. 16, lines 469-470

p. 18, lines 524-525

Delete the phrase, "*if relevant to the finished dosage form performance.*"

Rationale -- The drug substance manufacturer does not have the responsibility to determine the relevance to the finished dosage form performance. The finished dosage form manufacturer is responsible for the performance for the drug product.

p. 15, lines 433-435

p. 16, lines 472-474

p. 18, lines 528-530

When equivalence is not established, the need for qualification of impurities and studies to ensure bioequivalence of the dosage form should be considered.

This sentence should be changed to read. "When equivalence is not established, the need for qualification of impurities and studies to ensure bioequivalence of the dosage form should be considered **by the applicant**."

Rationale -- The drug substance manufacturer does not have the responsibility for considering the need to perform a bioequivalence study. The finished dosage form manufacturer is responsible for this determination.

p. 17, lines 477-478

- *A Certificate of Analysis from the supplier for each outsourced intermediate affected by the process change.*

As discussed under p. 10, lines 305-306, NAPM does not understand how the outsourced intermediate is affected by the scale change. Normally, a certificate of analysis is obtained from the outsource supplier.

p. 18, lines 503-505

A change-control protocol is a current GMP/SOP issue.

p 22, Attachment B

A definition for the term, "raw materials" should be added to this section.

PhRMA Bulk Active Postapproval Changes (BACPAC) Decision Tree

PhRMA Bulk Active Pharmaceutical Committee

For several years industry and FDA have reexamined the requirements for reporting postapproval changes. Recently, experts have held important discussions about the reporting requirements for postapproval changes in the manufacture of active pharmaceutical ingredients — bulk active postapproval changes (BACPAC). This article reflects the consensus position of PhRMA member companies with respect to such changes.

PhRMA BACPAC Work Group

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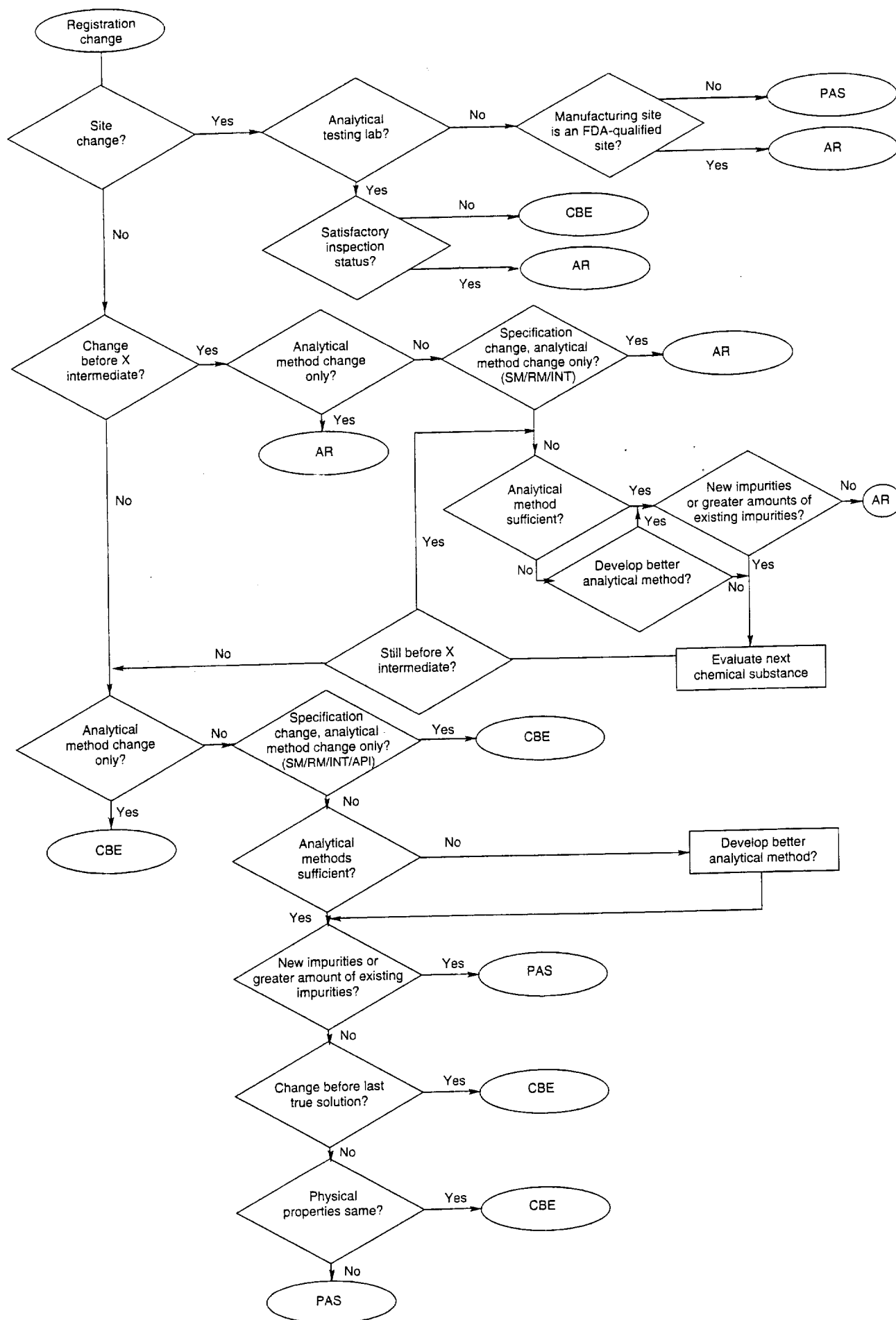
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During the past several years industry and FDA have worked together to reexamine the requirements for reporting postapproval changes. The overall effort to reinvent government operations created the opportunity to refocus on regulatory relief. The first in the series of scale-up and postapproval changes (SUPAC-IR) set the stage and suggested methods for regulatory relief for immediate-release oral drug products. Since then regulatory agencies have initiated other documents covering postapproval changes. Recently, experts have held important discussions about the reporting requirements for postapproval changes in the manufacturing of active pharmaceutical ingredients — bulk active postapproval changes (BACPAC).

This article reflects the consensus position of PhRMA member companies with respect to changes in an approved registration for active pharmaceutical ingredients (also referred to as drug substances). A drug substance is typically a well-characterized molecule prepared by a unique sequence of chemical reactions. A drug product combines drug substances with inactive excipients in a dosage form (e.g., tablet, capsule, or suspension) and is prepared by standard operations. A drug substance is defined by its chemical structure and its associated chemical and physical properties, whereas the properties of a drug product are linked to its manufacturing process. The current article presents an approach for evaluating a manufacturing change by using a data-driven scientific comparison of material prepared in the absence of (pre-) and using (post-) the proposed change. This comparison focuses on the ability of analytical techniques to detect changes in the quality attributes of intermediates and drug substances. Comparing the results from analyses of material prepared pre- and postchange allows manufacturers to assess the effect of a given change. In assessing these changes, firms are concerned not only about the regulatory issues but more importantly about the safety, efficacy, and quality of their products.

The decision tree presented here is arranged from the perspective of supporting a change in the approved NDA regis-



Definitions for decision tree

| | |
|--------------------|--|
| API | active pharmaceutical ingredient |
| FDA qualified site | currently manufacturing/testing an FDA-approved product/intermediate, which uses a similar process or technology, and has a current satisfactory GMP inspection by FDA or a governmental authority recognized by FDA |
| AR | annual report |
| CBE | changes being effected supplement |
| PAS | prior approval supplement |
| X intermediate | well-characterized, isolated intermediate which requires chemical bond formation/breaking to convert to drug substance, may be the last intermediate |
| SM/RM/INT | starting material/raw material/intermediate |
| last true solution | the processing point at which the drug substance is completely dissolved for the last time |

tration. The outcomes of the decision tree are regulatory reporting recommendations based on present postapproval filing mechanisms. Each change is correlated with the probability of affecting the drug substance and/or drug product. Those changes with a low probability of influencing the drug substance should be reported in annual reports (AR). Those with a high probability of impact should require prior approval supplements (PAS). Those in between require changes being effected (CBE) supplements.

The decision tree covers all processing steps in the preparation of drug substances produced by chemical synthesis, including chemical transformation of fermentation-derived substances. The changes include, but are not limited to, manufacturing site, materials used, equipment, scale, chemistry, processing operations, and testing methods. Although the specifics may be different for some operations such as fermentation or biotech drug substances, the overall approach is the same. Biologics that are not well characterized fall outside the scope of this decision tree because it is based on the use of analytical testing to show equivalence. Evaluating change in this manner (i.e., assessing the effect of change via a data-driven analysis) relies on analytical tools to evaluate impurity profiles and physical properties. The evaluation is also supported by a scientific understanding of the relevance of changes in various portions of a process based on the extensive experience with that process. GMP issues, validation, stability protocols, retest dating, and packaging are also outside the scope of this decision tree.

Imbedded within the decision tree is the concept of evaluating a material pre- and postchange. This evaluation depends on proper analytical methods as well as proper criteria. Depending on the specific change and good science, the proper criteria in-

clude established specifications and an evaluation of new impurities or greater amounts of existing impurities using ICH impurity guidelines. Criteria for physical properties may include established specifications as well as comparisons with previous process capabilities. Proper analytical methods include existing methods and additional appropriate methods needed to evaluate impurities and physical properties. For example, if a material's purity is determined by titration only, additional techniques are required to provide an impurity profile comparison.

As the decision tree indicates, the evaluation occurs as close as possible to the actual point of change, thus ensuring that the most meaningful data are evaluated. The data used to evaluate the change should be incorporated into any registration filing for that change.

ORGANIZATION

The decision tree can be divided into four major areas: the initial decision phase, changes involving site changes, changes before a demarcation point in the synthesis, and changes beyond that demarcation point in the synthesis. Each area has a consistent thought process. In general, changes can be evaluated within each area on a stand-alone basis. Some examples of change, however, must be evaluated in more than one area. In these cases each aspect should be independently evaluated with the most restrictive reporting requirement applied for a regulatory filing.

INITIAL DECISION

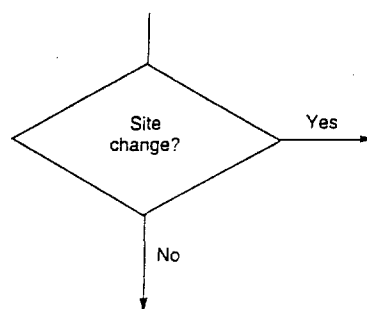


The starting point for the decision tree is the potentially difficult decision about the significance of a particular change. Existing regulations provide direction and requirements about when changes need to be reported for approved registrations. In fact, 21 *CFR* 314.70(a) begins with the following:

Changes to an approved application. The applicant shall notify FDA about each change in each condition established in an approved application beyond the variations already provided for in the application.

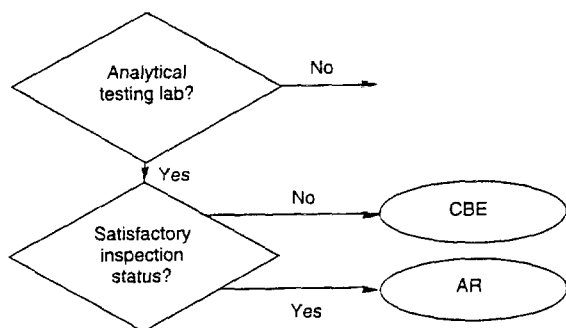
The first decision thus focuses on the change and the content of the approved application. If the change requires a modification to the registration, then the decision tree would apply. If the change does not require a change to the application, the decision tree would not apply for determining the reporting mechanism.

SITE CHANGE

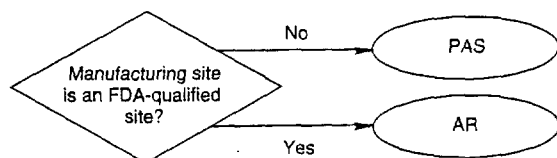


For drug substance operations, sites are generally identified in registrations as manufacturing sites and/or control facilities.

Testing facilities generally are either specifically identified or are assumed to be part of the manufacturing site, which includes control facilities

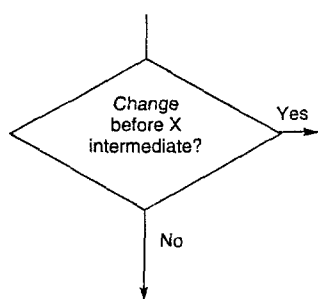


for raw materials, in-process testing, and drug substance release and/or stability. If the site change involves a change in the testing facility or the addition of another testing site, an AR would apply for testing laboratories with current satisfactory FDA inspection status, and a CBE would be appropriate for a testing laboratory without this status. GMP considerations of IQ/OQ and site qualification for the analytical methods being transferred would be independent of registration activities.



If the change involves a manufacturing site change, the decision centers around the status of the new site. An FDA-qualified site is one that currently manufactures an FDA-approved product or intermediate which uses a similar process or technology and has a current satisfactory GMP inspection (i.e., no regulatory action pending) by FDA or a governmental authority recognized by FDA. Assuming there are no other changes, the significance of the manufacturing site change is low, and the effect on the substance would be low. If this is the case, reporting can be done in an AR. This assumption includes equivalence of the process, equipment, materials, and quality systems. If these conditions are not met, then additional changes must be evaluated in other portions of the decision tree. If the new site is not FDA qualified, a PAS is required to ensure the opportunity for FDA compliance evaluation. In either case, data supporting such a change should be consistent with the processing step and the decision tree.

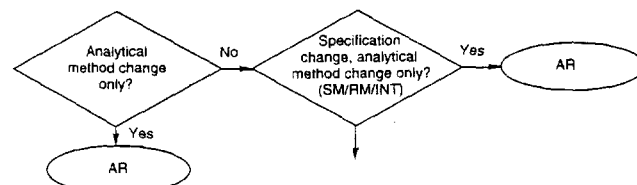
CHANGES MADE BEFORE AN X INTERMEDIATE



process steps. Many groups have identified this intermediate by various terms, each with slightly different definitions, result-

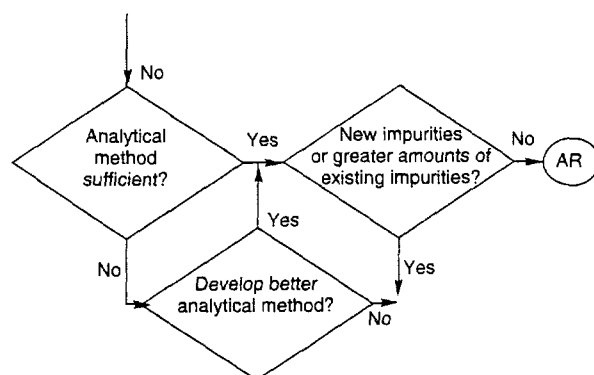
Experts generally agree that in a multistep chemical synthesis, changes made in early steps present a lower risk of affecting the drug substance than do changes made in late steps. For each synthesis there is an intermediate that represents the transition from early process steps to late

ing in confusion and a lack of consensus. Rather than using an existing term, *X intermediate* will be employed to focus on the concept of the characteristics of that intermediate. The *X intermediate* is the last well-characterized, isolated intermediate before the formation of the active molecule (i.e., a molecule that requires chemical bond formation or breaking to form the final drug substance, i.e., not a salt). In a linear synthesis the *X intermediate* may be the last isolated intermediate before the drug substance. In a convergent synthesis — in which two isolated intermediates are being reacted together to form the drug substance molecule — both intermediates would be defined as *X intermediates*.

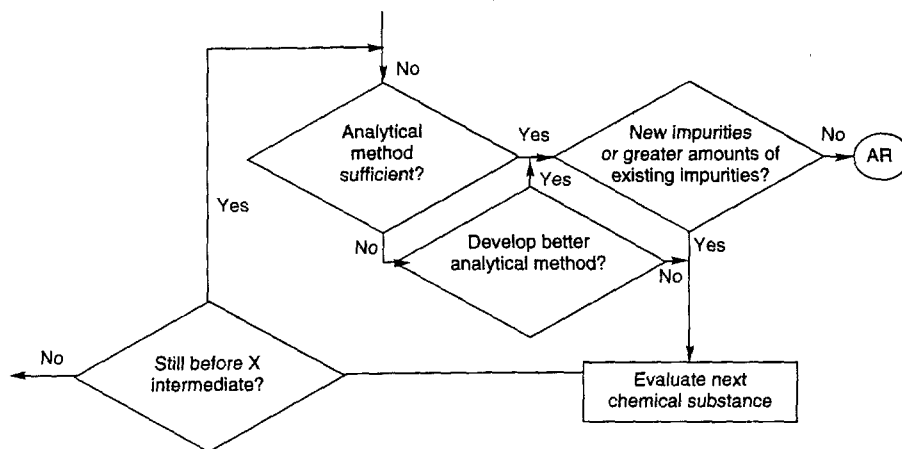


Bearing in mind this definition of an *X intermediate*, clearly one major category is that of changes before the *X intermediate*. There are two sets of changes within this category: one that comprises analytical method and/or specification changes only (i.e., no changes in the processing of any material) and the other dealing with actual changes in the operations. If there is only an analytical method change and all else remains consistent, the change would have low probability of affecting the drug substance (it is before an *X intermediate*) and would be consistent with AR requirements.

If a specification needs to be tightened or loosened for a starting material, raw material (including solvents), or intermediate, the decision must focus on the reason for the change. If the specification change is required only because a manufacturer is using a new analytical method that is equivalent to or better than the existing method without changing the material or process, then because this change is before the *X intermediate* the probability of affecting the drug substance is low and would be consistent with AR requirements. If the specification change is required because of an actual change in the operations, then further evaluations are necessary.



As discussed in the introduction, the fundamental advantage of evaluating changes in drug substance processing is the availability of many analytical tools. To that end, if there is an actual change of any type in the process, the primary decision depends on the adequacy of the analytical methods used to determine equivalence. Validated and suited for the intended

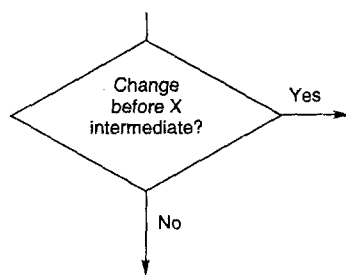


use, analytical methods (e.g., an assay method and impurity profile methods) should be available to evaluate the purity of the chemical substance. The impurity profile methods should have appropriate quantitation limits and should be specific not only for known impurities but also for potential new impurities based on the nature of the change. Methods that permit testing for specific solvents, reagents, or catalysts used in processing should also be available. If the analytical methods are scientifically sufficient, the evaluation compares the material produced with and without the change.

The decision focuses on new impurities or greater amounts of existing impurities. If there are no new impurities (organic, inorganic, residual solvents) greater than the ICH guidelines for qualifying impurities and if there are no greater amounts of existing impurities (based on process history), then the change would have a low probability of affecting the safety of the drug substance and would be consistent with AR requirements.

On the other hand, if there is a new impurity or if the amounts of existing impurities are greater than those specified in the ICH guidelines, then the material pre- and postchange is not equivalent at this processing stage. The significance of this fact must be evaluated by examining the next chemical substance. If this step is still before the X intermediate, then this approach is repeated at the next step in the synthesis. If it is not, then considerations proceed to the next stage of the decision tree.

CHANGES AFTER AN X INTERMEDIATE

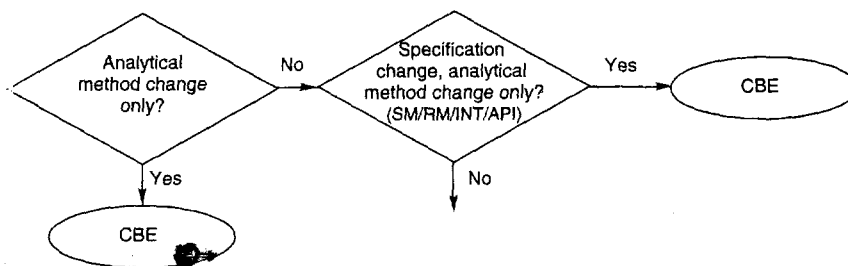


The item named, "Changes before X intermediate?" represents a significant break in the decision tree. Changes from the point of an isolated X intermediate through to the drug substance are viewed differently from the standpoint

of the probability of affecting the impurity profile or physical properties of the drug substance.

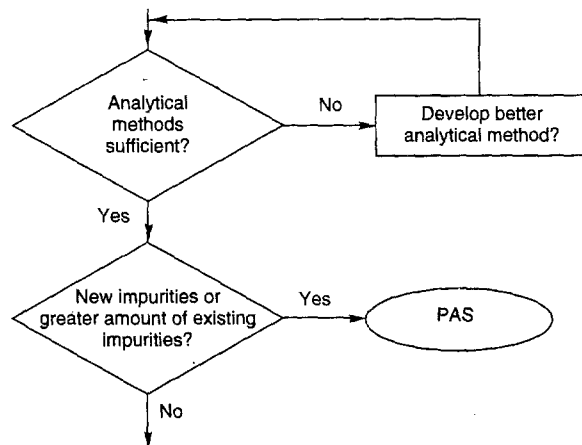
As with changes before the X intermediate, changes can affect the analytical methods and/or specifications only (i.e., no changes

in the production of the material) or can represent actual changes in the operations. If the change is an analytical method change only (i.e., use of an equivalent or better method) then the probability of affecting the drug substance is low. Because this change is beyond the X intermediate, a CBE supplement is recommended. An analogous situation would be a change to a specification of a material in this portion of the synthesis (starting material, raw material, intermediate, or even drug substance) in which case the specification change is driven only because of a change in the



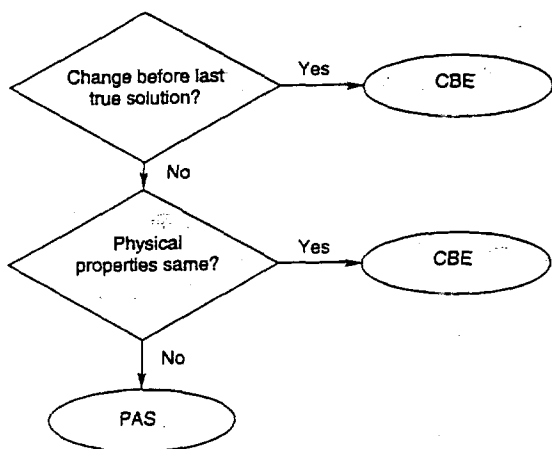
analytical method without a change in the manufacturing operations. Reporting this type of change via a CBE supplement would be consistent with the low potential effect of this change.

On the other hand, if there is a processing change the manufacturer must address the question of impurities. As in the sections before the X intermediate portion of the decision tree, the manufacturer must examine the adequacy of the analytical methods for



existing and new impurities. Additional or improved analytical methods are necessary if the existing methods are inadequate. If the methods are scientifically acceptable, the company must evaluate the impurity profile while considering ICH guidelines. If there are new impurities or greater amounts of existing impurities, the change represents a high probability of affecting the drug substance. If the manufacturer decides to implement the change, reporting via a prior approval supplement (PAS) is consistent.

Even if the impurity profile change would lead to a PAS, a manufacturer may also need to assess the effect of the change on



a substance's physical properties. To do this, the manufacturer must determine if the change is before the processing point at which the drug substance is completely dissolved for the last time (referred to as the last true solution). Physical properties of the drug substance are established after the last true solution.

For a change that occurs after the X intermediate and before the last true solution, if appropriate analytical methods determine that there has been no negative effect on the impurity profile, the change has only a very low probability of influencing the drug substance. In this case, a CBE supplement would be sufficient without the need to wait for prior approval. If the

change is after the last true solution but the analytical results show that the physical properties pre- and postchange are unchanged, then a CBE supplement is also consistent with the low probability of affecting the drug substance. If the physical properties are different, however, then the probability of influencing the drug product is high, and a PAS is appropriate.

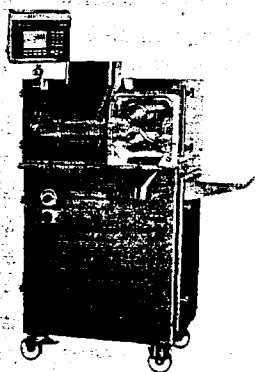
SUMMARY

The PhRMA BACPAC decision tree outlines a unified approach that uses scientific assessment and historic experience for evaluating postapproval changes in drug substance manufacturing. The recommended regulatory reporting mechanisms reflect the major vs. minor impact of changes on the quality of the drug substance or an intermediate.

ARs and CBE supplements are suitable when manufacturing changes result in chemical substances that meet established specifications, along with impurity profile and physical property (only for changes after the last true solution) comparison criteria. Prior approval supplements are recommended only for changes that negatively affect the quality of the drug substance or for a manufacturing site change that necessitates a GMP inspection (i.e., the manufacturing site is not FDA qualified). This approach provides a consistent strategy that is based on the assessment of major vs. minor effects on the overall quality of the chemical substances resulting from bulk drug manufacturing changes, as opposed to attempting to categorize types of change themselves as major or minor. □

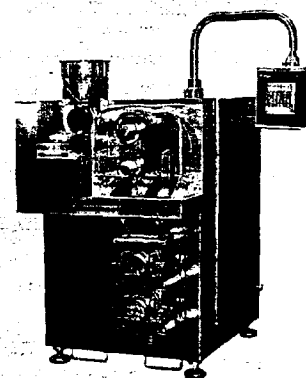
NEW ROLLER COMPACTOR MODELS

WP 120 & WP 200



WP 120 Lab Unit

- ❖ GMP Monoblock Design
- ❖ Vacuum Deaeration Feed Screw System
- ❖ Removable, Cantilever Rollers
- ❖ PLC Controlled
- ❖ Integrated 2 Stage Size Reduction



WP 200 Production

In addition to roller compaction, our equipment range includes size reduction, extrusion, moist granulation, and grating/shredding machinery. Tests & technical services are available from our Horsham, Pennsylvania facility or our headquarters in Germany. We offer over 110 years of process, engineering, and equipment experience. Contact us for more details.

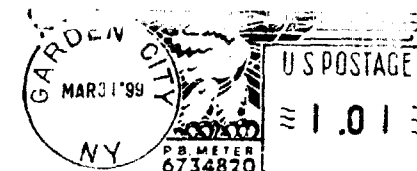
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